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Glucose metabolism in nerve terminals

Ghazaleh Ashrafi and Timothy A. Ryan

Department of Biochemistry, Weill Cornell Medical College, New York, USA

Abstract

Nerve terminals in the brain carry out the primary form of intercellular communication between neurons. Neurotransmission, however, requires adequate supply of ATP to support energetically demanding steps, including the maintenance of ionic gradients, reversing changes in intracellular Ca^{2+} that arise from opening voltage-gated Ca^{2+} channels, as well recycling synaptic vesicles. The energy demands of the brain are primarily met by glucose which is oxidized through glycolysis and oxidative phosphorylation to produce ATP. The pathways of ATP production have to respond rapidly to changes in energy demand at the synapse to sustain neuronal activity. In this review, we discuss recent progress in understanding the mechanisms regulating glycolysis at nerve terminals, their contribution to synaptic function, and how dysregulation of glycolysis may contribute to neurodegeneration.

Introduction

All tissues in the body rely on oxidation of a carbon-rich source to generate the key high-energy intermediate, ATP, to fuel biochemical processes. In the brain, this is generally limited to the use of glucose, while other tissues can also utilize oxidation of other fuels such as fatty acids, hence glycolysis is of central importance to brain function. Furthermore, the adult human brain consumes 20% of the total energy in the body while it comprises only 2% of the body weight[1]. Thus at the whole organism level, much of the “metabolic wiring” is dedicated to ensure adequate glucose supply for the brain as failure to do so can have drastic consequences. A rapid decline in brain glucose levels for example, as experienced during insulin-induced severe hypoglycemia, typically leads to cognitive dysfunction such as seizures and coma. Interestingly, several tissues in the body have high energetic needs that must be met by appropriate delivery of fuel to maintain function. For example, the heart is continuously beating and at any one time at least some neurons in the brain are firing, thus these tissues are never in a truly resting state. Furthermore, both tissues undergo rapid changes in function since cardiac workload can vary significantly during exercise, and individual neurons undergo rapid changes in action potential firing during specific cognitive tasks. A critical question therefore is, how is the production of ATP regulated rapidly enough to match changes in neuronal function?

Corresponding author: Ryan, Timothy A. (taryan@med.cornell.edu).

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Questions about Brain Glycolysis

As glucose is the typical carbon source used to fuel brain metabolic needs, there are a number of important questions that arise to understand its mechanistic basis and significance: What cells in the brain carry out the combustion of glucose, and how is it regulated? Does the full combustion of glucose to CO_2 and H_2O , through oxidative phosphorylation (OxPhos), occur in the same cells where glycolysis occurs? Are there backup systems that can maintain function when the supply of glucose is interrupted? What happens when these backups are depleted?

In this review, we will examine these problems with an emphasis on recent progress in understanding the mechanisms regulating local energy production at the synapse and their contribution to synaptic function. In addition, we will address how dysregulation of energy metabolism in distal axons contributes to neurodegeneration.

6 carbons or 3?

Glucose consumption is a signature of brain activity and is used extensively in functional brain imaging techniques such as positron emission tomography. However, the exact identity of activity-dependent metabolic processes as well as the cell types consuming glucose remain poorly understood. In particular, it is not clear whether neurons primarily utilize glucose or lactate during periods of intense firing. In the astrocyte-neuron lactate shuttle (ANLS) model put forward by Magistretti and colleagues[2], the glutamate released from active neurons stimulates astrocytes to take up glucose and glycolytically metabolize it to lactate. Lactate is then exported to neurons, where it is converted to pyruvate to fuel OxPhos. The ANLS model thus suggests that lactate, not glucose, provides energetic support for firing neurons. The model also predicts that the majority of ATP production in active neurons is met through mitochondrial oxidative phosphorylation (OxPhos) with glycolysis playing only a secondary role. The sharing of lactate between cell types has been known for many decades and forms the basis of the Cori cycle, whereby excess pyruvate produced in muscle is recycled in the form of lactate back to the liver where it is used in gluconeogenesis [3]. Although there are a number of compelling reasons to think that such lactate sharing occurs between astrocytes and neurons, we present here several lines of evidence that neurons, and in particular nerve terminals, likely rely on local glycolysis:

1. ATP supply is rapidly regulated to meet needs

The vulnerability of the brain to metabolic defects, even on very short time scales, indicates that even if the brain can tap into backup sources of carbon to produce ATP, it is either too slow or insufficient in capacity to meet the ongoing needs of neuronal function. We recently showed, for example, that although completely blocking glycolysis leads to only a slow decline in ATP levels in resting neurons, this critical metabolite drops precipitously if glycolysis is blocked during activity, leading to rapid inhibition of presynaptic function[4]. These results led us to conclude that glycolysis is controlled by activity and failure to do so quickly would be catastrophic for synaptic transmission[4]. The tightness of this coupling also argues against a simple reliance on astrocytic glycolysis and a lactate shuttle since it would require buildup of lactate in the extracellular space which would likely be too slow to

support continuous synaptic communication[5]. In contrast, glycolytic ATP production is thought to be relatively fast[6]. These observations clarify the need to properly understand how activity, which drives ATP consumption, is coupled to the generation of ATP via glycolysis in neurons.

2. Enrichment of the glycolytic machinery in presynaptic compartments

Biochemical purification of synaptosomes and synaptic vesicles (SVs) has demonstrated that 5 of the 10 known enzymes that convert glucose into pyruvate are specifically enriched on SVs[7–9], several of which are specifically associated with the energetic payoff steps in glycolysis. Such localization has led to the speculation that locally produced ATP maybe handed off directly to ATP consuming enzymes such as the V-type ATPase on SVs that helps power neurotransmitter filling. Glycolytic enzymes are also shown to be physically associated with the Na⁺/K⁺ pump in erythrocytes[10] (and possibly in neurons[11]), as well as with axonal transport organelles[12], allowing for rapid and local powering of energy-consuming processes. Our own measurements demonstrate that if presynaptic glycolysis is inhibited, endocytosis of SVs is blocked, indicating that one of the molecular steps associated with membrane fission is highly reliant on rapid ATP generation[4].

3. Local glycolytic metabolon formation during energy stress

More recently, a genetic screen aimed at identifying the protein machinery essential for maintaining presynaptic organization demonstrated that during periods of energy stress a local metabolon is formed at presynaptic boutons[13] (Fig. 2B). The metabolon refers to a local increase in the concentration of a number of glycolytic enzymes, specifically, phosphofructokinase, aldolase, glyceraldehyde-3-phosphate dehydrogenase, pyruvate kinase, and this enzyme clustering is essential for SV recycling[13] (Fig. 2E).

4. Expression and regulation of neuronal glucose transporters

Neurons have long been known to have high expression of Glut3[14] suggesting that glucose uptake is primarily mediated through this transporter. Two recent studies also shown that perfusion of extracellular glutamate triggers surface accumulation of Glut3 in soma and dendrites, potentially mitigating excitotoxic effects by increasing glucose utilization[15,16]. A different glucose transporter, Glut4, known for its insulin-mediated glucose uptake in adipocytes and muscle[17], is expressed in many brain regions[18,19], however the functional role of Glut4 in brain metabolism is not understood. We demonstrated that Glut4 is recruited to the surface of presynaptic endings in firing neurons to increase glucose uptake and consequently upregulate glycolysis during activity[20] (Fig. 1 and 2A). Functionally, Glut4-mediated upregulation of glycolysis is essential for SV recycling during neuronal activity (Fig. 2E), thereby highlighting the crucial role of glycolytic regulation in synaptic function. Consistent with our Glut4 study, a new report indicates that hippocampal Glut4 translocates to the plasma membrane after memory training and is involved in long-term memory formation[21].

The data presented in each of the aforementioned points strongly suggest that glycolytic enzymes are favorably positioned in presynaptic endings to rapidly metabolize glucose during activity to fuel key steps in synaptic vesicle recycling.

Regulation of neuronal glycolysis

The increased rate of glycolysis driven by electrical activity results in part from increased import of glucose, that in turn is driven by the metabolic feedback regulator AMP kinase[20]. At present, the relevant substrate(s) for AMP kinase that mediate Glut4 translocation in axons are not known, but in muscle AMP kinase controls the activity of a Rab GAP[22]. Expression of the relevant muscle Rab GAP in neurons where the serines that are substrates of AMP kinase have been mutated to alanine, blunt the ability of electrical activity to mobilize Glut4[20], and thus it seems likely that axons utilize a machinery similar to that in exercising muscle to regulate glycolysis. One potentially important but relatively poorly explored feature of glycolysis is that it can only proceed if there is sufficient supply of the essential electron acceptor nicotinamide adenine dinucleotide (NAD^+). The oxidation of each glucose molecule requires two NAD^+ molecules (that are reduced to NADH) in a reaction catalyzed by glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Therefore to sustain glycolysis, NAD^+ needs to be continuously replenished from one of three sources: 1) NAD^+ can be synthesized through nicotinamide biosynthetic pathways (see below); 2) NAD^+ can be regenerated with the conversion of pyruvate to lactate by lactate dehydrogenase, in turn diverting pyruvate away from OxPhos; 3) NAD^+ can be replenished by 2 different shuttle systems in the mitochondrial inner membrane whereby electrons from the cytosol are transferred to the mitochondrial matrix (the malate-aspartate shuttle and the glycerol-3-phosphate shuttles)[23] (Fig. 3). Interestingly, both of these shuttles appear to be upregulated by cytoplasmic Ca^{2+} [24,25], providing a potential feed-forward regulation between electrical activity and glycolysis, and they are required for Ca^{2+} -driven mitochondrial respiration in active neurons[26]. Since the ability to transfer electrons into the electron transport chain depends on the state of mitochondrial respiration, these shuttles also potentially provide another link coupling glycolysis and OxPhos[27](Fig. 3C–D).

Backup supplies?

Many tissues in the body rely on the ability to tap into stored carbon sources (e.g. fatty acids, and glycogen) to supplement energy needs during periods of compromised carbon input. Neurons however do not express key enzymes either necessary for β -oxidation (the catabolism of fatty acids to acetyl-coA) or glycogen formation or use, although these enzymes are expressed in astrocytes[28,29]. One might expect, therefore, that the ANLS might be particularly important in allowing neurons to signal to astrocytes to mobilize glycogen stores and deliver lactate during periods of reduced carbon supply.

Glycolytic compromise and neuronal dysfunction

It is interesting to note that certain drug-resistant forms of epilepsy, particularly in children, can be effectively treated by switching to a highly ketogenic diet, where glycolysis would be bypassed in favor of OxPhos[30]. Although the mechanistic basis for this dietary remedy is poorly understood, we speculate that compromise in glycolytic throughput, given its tight coupling to SV recycling, would potentially dampen sustained high-frequency firing and seizure propagation[20,31].

The importance of sustaining NAD⁺ levels (and therefore likely glycolysis and ultimately ATP levels) has also been shown to be a central tenet of axon survival following axotomy. NAD⁺ can be synthesized from various precursors, mediated by the enzymatic activity of nicotinamide mononucleotide adenylyl-transferase (Nmnat)[32]. Similar to energy deprivation[33], loss of one of the three mammalian Nmnat isoforms (Nmnat2) leads to neuronal degeneration[34]. Furthermore, a chimeric gene (*Wld^S*) containing the coding sequences of a ubiquitin ligase and *Nmnat-1* protects injured axons from Wallerian degeneration, in which the distal portion of a severed axon degenerates in a stereotyped manner[32]. Similar to the *Wld^S* mutant, Nmnat overexpression[35] or exogenous supplementation of nicotinamide[36] are sufficient to rescue Wallerian degeneration, suggesting that the protective effects of Nmnat can be attributed to local NAD⁺ synthesis in axons. In degenerating axons, NAD⁺ levels decline first, driven by unknown mechanisms involving the protein SARM, followed by ATP levels[36,37], further relating NAD⁺ to energy metabolism and neuronal survival. In fact, a recent study concluded that Wallerian degeneration may specifically disrupt glycolysis in axons[38]. Taken together, these findings are consistent with a model whereby Nmnat expression rescues axon degeneration by preventing a decline in NAD⁺ level, thereby sustaining ATP production through glycolysis.

Collectively, the findings presented here indicate that glycolysis plays a significant role in presynaptic and axonal metabolism and is precisely regulated to meet energetic demands of synaptic function. Understanding the regulation of neuronal glucose metabolism is of particular importance as there is mounting evidence linking dysregulation of neuronal energetics to neurodegeneration.

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- Neuronal activity upregulates glycolysis at nerve terminals.
- Glycolysis is essential for synaptic function.
- The availability of the cofactor NAD^+ may be a limiting factor for glycolysis and ATP production in neurons.

Figure 1. Glut4 vesicles rapidly insert into the presynaptic plasma membrane in response to neuronal firing

(A) Schematic drawing of the use of Glut4 tagged with pHluorin (pH) to visualize its trafficking in neurons. pHluorin is pH sensitive and its fluorescence is quenched in the acidic environment of endosomes but not when exposed to extracellular space. (B) Glut4-pH fluorescence (pseudocolor) increases in presynaptic boutons (arrowhead) after electrical stimulation with 600 action potentials (APs). (C) Average trace of Glut4-pH in response to stimulation. (Adapted from [20]). Gray lines are standard errors. Scale bar, 5 μ m.

Figure 2. Neuronal activity stimulates glycolysis in presynaptic boutons

(A) Presynaptic APs drive the translocation of the glucose transporter Glut4 to the membrane where it increases glucose uptake. (B) Activity also stimulates the formation of a cluster of glycolytic enzymes (metabolon) that can rapidly metabolize glucose. (C) Glycolysis results in the production of pyruvate, a substrate for mitochondrial OxPhos, (D) which together with glycolysis produces ATP (E) to power the recycling of SVs following their release during synaptic activity.

Figure 3. The central role of NAD^+ shuttle systems in glucose metabolism

(A) The malate-aspartate (MA) shuttle uses cytoplasmic and mitochondrial malate dehydrogenases to convert aspartate to malate and NADH to NAD^+ in the cytosol, as well as the reverse in the mitochondrial matrix. Malate and aspartate are exchanged between the two compartments by the malate/ α -ketoglutarate and the aspartate/glutamate antiporters. (B) In the glycerol-3-phosphate shuttle, cytosolic glycerol-3-phosphate dehydrogenase converts NADH to NAD^+ and dihydroxyacetone phosphate to glycerol-3-phosphate while the mitochondrial enzyme reverses the reaction releasing electrons to the electron transport chain. The cytosolic NAD^+ produced by the shuttles serves as cofactor driving glycolysis, while (C) mitochondrial NADH produced by the shuttles and the TCA cycle drives the formation of a proton gradient by the electron transport chain (D) which is then used by the F_1F_0 -ATPase to synthesize ATP. Asp: aspartate; Glu: glutamate; cMDH, mMDH: cytoplasmic and mitochondrial malate dehydrogenase; α -KG: α -ketoglutarate; G3P: glycerol-3-phosphate; DHAP: dihydroxyacetone phosphate; cGPDH and mGPDH:

cytoplasmic and mitochondrial glycerol-3-phosphate dehydrogenase; ETC: electron transport chain. TCA cycle: tricarboxylic cycle.

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